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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,332	04/07/1999	KAARE M. GAUTVIK	16777/309	6190

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/287,332	Applicant(s) GAUTVIK ET AL.	
	Examiner Robert Landsman	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-56* is/are pending in the application.

4a) Of the above claim(s) *21-23,30-33 and 48-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-29,34-47 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Formal Matters

A. Amendment D, filed 11/29/01, has been entered into the record.

B. Formal Drawings, filed 11/29/01, have been entered into the record and have been approved by the draftsman.

C. Claims 24-29 and 34-37 were under consideration in this application. New claims 38-56 have been added. Therefore, claims 24-29 and 34-56 are currently under consideration. Newly submitted claims 48-51 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims of the elected invention, 24-29, 33-47 and 52-56, are drawn to compositions comprising wild-type hPTH whereas claims of the non-elected invention, 21-23, 30-33 and new claims 48-51 are drawn to hPTH with a mutation in one of the amino acid residues.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims48-51 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

Objections

A. The objections to the specification have been withdrawn in view of Applicants' amendments to pages 8 and 9 of the disclosure.

B. The objections to the drawings have been withdrawn since Applicants have amended the Brief Description of Drawings to correspond to the Figures.

C. The objection to claims 27, 34 and 36 under 37 CFR 1.75 as being substantial duplicates has bee withdrawn since these claims each recite limitations not found in the other claims.

D. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required: there is no antecedent basis in the specification for the recitation of "greater than 90%" purity of the claimed protein.

E. The disclosure is objected to because of the following informalities; Appropriate correction is required for each of the following items:

The information at page 1, lines 20-23 appears duplicative of the first paragraph of the same page.

Claim Rejections

1. Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. The rejection of claims 34 and 35 under 35 USC 112, first paragraph, regarding "optimized consensus sequence" has been withdrawn since Applicants provide a written description of this sequence on pages 24, lines 7-26 of the specification.

B. Claims 34 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "optimized consensus signal sequences" of claims 35 and 53 for expression in Saccharomyces, does not reasonably provide enablement for all "optimized consensus signal sequences" in all microorganisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The breadth of claims 34 and 52 is excessive. Applicants have only provided a minimum of guidance and working examples of "optimized consensus signal sequences" for protein expression in

different microorganisms and, similarly, the "optimized" sequences would be organism-dependent. The only limitations of these sequences in the claims is that they must comprise a positively charged amino-terminal, a hydrophobic core, and a polar COOH-terminal region. No other limitations are used to teach one of ordinary skill in the art how to make these optimized sequences, including a size limitation. Furthermore, it is not predictable to the artisan, even by using these limitations as recited in claims 34 and 52, which positive, hydrophobic and polar amino acids can be used to form a functional consensus sequence. Millions of possible combinations of these sequences are possible and Applicants have only taught 4 of these sequences.

Therefore, in summary, due to the excessive breadth of the claims regarding all "optimized consensus sequences" as well as the minimal guidance and working examples of these sequences along with the lack of predictability to the artisan how to make a functional "optimized consensus signal sequence" other than that for Saccharomyces, the Examiner holds that undue experimentation would be necessary to practice the invention as claimed.

C. Claims 24-29, 34-47 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Saccharomyces mating factor α1 leader sequence which is cleaved in the yeast cells exemplified in the specification, does not reasonably provide enablement for all leader sequences for use in all microorganisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The breadth of the claims is excessive regarding the use of all microorganisms other than yeast to produce hPTH, as well as for leader sequences other than Saccharomyces mating factor α1 leader sequence within the metes and bounds of the formula of claim 24 for use in organisms other than yeast. Applicants are enabled for the use of leader sequences for use in expressing hPTH in yeast. However, Applicants are not enabled for the use of leader sequences in microorganisms other than yeast. Applicants have provided no guidance or working examples of organisms other than yeast which can be used to express hPTH. Furthermore, it is not predictable to one of ordinary skill in the art how to make a leader sequence within the metes and bounds of the formula of claim 24 which can be used to express hPTH in an organism other than yeast, nor is it predictable in what microorganisms other than the disclosed yeast strains leader sequences other than Saccharomyces mating factor α1 leader sequence can be used. Similarly, it is not predictable how to make any generic leader sequence, as recited in, for example, claims 34 and 36.

In summary, the breadth of the claims is excessive regarding the use of all microorganisms, other than yeast, to produce hPTH as well as the use of leader sequences other than that within the metes and bounds of claim 24, to produce hPTH in organisms other than yeast. This, in addition to the lack of guidance and working examples of organisms other than yeast in which leader sequences can be used to produce hPTH, along with the unpredictability of how to make and use these leader sequences in organisms other than yeast, leads the Examiner to hold that undue experimentation is required to practice the claimed invention.

2. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. The rejection of claim 24 under 35 USC 112, second paragraph, has been overcome since Applicants have amended the claim to recite "STE13 recognition site." However, new claim 42 is now rejected under 35 USC 112, second paragraph, for this reason since it recites "STE13 recognition."

B. The rejection of claims 24-29 and 34-37 under 35 USC 112, second paragraph, regarding "composition comprising" has been withdrawn since, as Applicants have argued, this is an open-ended recitation and, therefore, not indefinite.

C. Claims 24-29 and 34-37 remain rejected under 35 USC 112, second paragraph, regarding the cleaving of the leader sequence from PTH and new claims 38-47 and 52-56 are also rejected. Applicants have argued and demonstrated, the leader sequences are cleaved and provide support on page 6, lines 25-28 of the specification. However, the specification only provides support for the cleaving of this leader sequence in yeast, and not in other microorganisms. Since the claims do not limit this process of producing hPTH to yeast, it remains unclear how and where this leader sequence is cleaved.

D. The rejection of claims 26 and 29 under 35 USC 112, second paragraph, regarding "90% purity" has been withdrawn since Applicants have amended the claims to recite that the protein of claim 24 part (c) is purified to greater than 90%.

E. The rejection of claim 29 under 35 USC 112, second paragraph, regarding "the protein" has been withdrawn since Applicants have amended the claim to recite "said hPTH."

F. The rejection of claim 34 under 35 USC 112, second paragraph, regarding "optimized consensus sequence" has been withdrawn since, although broad, the claim is not indefinite as defined on page 24, lines 7-26 of the specification. Furthermore, the rejection of this claim regarding parts 2(i) – 2(iii) have been withdrawn since Applicants have amended the claim to clarify the DNA and protein components.

G. The rejection of claim 35 under 35 USC 112, second paragraph, regarding whether or not the recited consensus sequences are already optimized has been withdrawn since it is clear that they are optimized.

H. The rejection of claim 36 under 35 USC 112, second paragraph, regarding "the expression product" has been withdrawn since Applicants have removed this phrase from the claim.

I. The rejection of claim 36 under 35 USC 112, second paragraph, regarding "the expression product" has been withdrawn since Applicants have removed this phrase from the claim.

J. Claims 38, 41, 42, 45, 48, 52 and 54 are unclear since the word "component" is confusing. The word "component" could be interpreted as, for example, a hydrogen atom. It is suggested that the word, for example, "fragment" be substituted for the word "component" since this term is more understood in the art to mean one or more amino acids of a protein – **as long as no new matter is added**.

K. Claims 44 and 47 are confusing since it appears that this claim should be referring to part (d) of claims 43 and 45, respectively, not to part (c) since part (d) recites the purification step.

L. Claims 24-29, 34-37, 42-47 and 52-56 are confusing since it is not clear if the PTH is purified before or after it becomes part of the claimed composition. If the PTH is purified before it becomes part of the composition, it is not understood how this protein would remain pure once it becomes part of a composition.

3. Claim Rejections - 35 USC § 101 – statutory double patenting

A. The rejection of claims 24-26 of the present invention under 35 USC 101 as being unpatentable over claim 3 of the '242 patent has been withdrawn since, even though the claims of both the patent and the present application recite an intact hPTH, the present invention uses a microorganism to cleave the leader sequence from PTH, therefore, making it "clean."

4. Claim Rejections - 35 USC § 101 – obviousness-type double patenting

A. The rejection of claims 24-26 of the present invention under 35 USC 101 as being unpatentable over claim 3 of the '242 patent has been withdrawn since, even though the claims of both the patent and the present application recite an intact hPTH, the present invention uses a microorganism to cleave the leader sequence from PTH, therefore, making it "clean."

5. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 24-29 and 34-37 remain rejected under 35 USC 102(b) as being unpatentable over either Keutmann et al. or Kimura et al. and newly added claims 42-47 and 52-56 are also rejected for the reasons already of record on pages 8-9 of the Office Action dated 6/29/01. Applicants argue that the hPTH of the present invention is recombinant and, therefore, free of human contaminants whereas the hPTH of both Keutmann et al. or Kimura et al. are purified from human sources and, therefore, have contaminants not found in the recombinant PTH compositions of the present invention.

These arguments have been fully considered, but are not deemed persuasive. As stated in the above rejection under 35 USC 112, second paragraph, the claims of the present invention do not recite "purified hPTH," but, rather, "compositions comprising hPTH." Therefore, even if the hPTH of the present invention was purified 100%, once it is placed into a composition, the presence of other contaminants, including human contaminants that may be present in the compositions of Keutmann et al. or Kimura et al. would meet the limitations of the presently claimed invention.

B. Claims 24-29, 34-37, 42-47 and 52-56 are rejected under 35 USC 102(b) as being anticipated by either Brewer et al. (US Patent No. 3,886,132; reference A11 on Form PTO-1449), Kumagaye et al. (J.

Chrom. 327:327; reference A50 on Form PTO-1449) or Fairwell et al. (Biochem. 22:2691; reference A52 on Form PTO-1449).

The claims recite a composition comprising recombinant hPTH. However, the claims of the present invention do not recite "purified hPTH," but, rather, "compositions comprising hPTH." Therefore, even if the hPTH of the present invention was purified 100%, once it is placed into a composition, the presence of other contaminants, including human contaminants that may be present in the compositions of Brewer et al, Kumagaye et al., or Fairwell et al. would mean that these compositions of these meet the limitations of the presently claimed invention. However, Kumagaye et al. disclose the separation via cation exchange HPLC of two 84 amino acid forms of hPTH, Asn_{76} and Asp_{76}. The peptides were made synthetically (see end of first page), and, therefore, free of human contaminants, and were substantially pure, in view of the fact that separation of two such closely related species was possible. The use of HPLC inherently involves the use of a liquid to dissolve to PTH (i.e. composition).

Similarly, Fairwell et al. disclose solid phase synthesis, purification and characterization of hPTH (1-84) (see title, abstract). The protein appears to have been at least 95% pure on the basis of minimal (5-6%) residue preview on sequencing and biological activity (see page 2694). Therefore, the claimed compositions are anticipated by either Brewer et al, Kumagaye et al., or Fairwell et al.

6. Claim Rejections - 35 USC § 102/103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 24-29, 34-37, 42-47 and 52-56 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Brewer et al., U.S. Patent Number 3,886,132.

Brewer et al. disclose highly purified human PTH. See abstract, and col. 2 lines 49-60 wherein it is disclosed that the preparation was pure enough to sequence 34 amino acid residues starting at the amino terminus of the protein. Thus, the protein as purified by Brewer et al. appears to be consistent with the limitations of the instant claims with respect to being pure hPTH. It cannot be determined by the Examiner whether Brewer's protein specifically meets the limitations of being 90% pure, although it would seem likely that it did, given Brewer's ability to sequence 34 residues. It is noted that the only portion of the specification

which relates to purity is the disclosure that the protein was partially sequenced (page 7, starting at line 27), which the ordinary artisan would recognize as requiring a relatively pure preparation of the desired protein (although no exact percentage purity can be implied). Based upon the fact that the specification discloses obtaining the sequence of 19 and 45 amino acids respectively, from the yeast and E. coli-produced protein, Brewer's ability to obtain 34 amino acids would seem to indicate that comparable purity was achieved. The examiner is unable to determine whether the prior art disclosure possesses the unrecited characteristics or property. With these conditions, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

The decisional law has clearly emphasized that such claims are directed to a product and are not restrictive to a process because they are not construed as being limited to the product of a specific process (*In re Bridgeford*, 149 USPQ 55: *In re Hirao*, 190 USPQ 15). Patentability depends on whether the product is known in the art or obvious, and is not governed by its process of production (*In re Klug*, 142 USPQ 161); therefore, the burden is upon applicants to establish a patentable difference between the claimed product and that of the prior art (*In re Fessman*, 180 USPQ 324). Further held was that when a prior art product reasonably appears to be the same as that claimed, but differs by the process via which it was produced, a rejection of this nature is eminently fair and the burden is upon applicants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685; *In re Marosi*, 218 USPQ 289; *In re Thorpe*, 227 USPQ 965; *In re Fitzgerald*, 205 USPQ 594; and as more recently emphasized in *Ex parte Gray*, 10 USPQ 2d 1922; *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 9 USPQ 2d 1833; and *Scripps Clinic v. Genentech Inc.*, 3 USPQ 2d 1481). In view of the fact that the courts have clearly emphasized that product-by-process (p-b-p) claims are not patentable over product claims unless there has been established a patentable difference, one having ordinary skill in the art at the time of the invention would have expected that the hPTH produced by organic synthesis or by the recombinant process disclosed in the instant specification would be functionally/biologically equivalent to native hPTH as purified by Brewer et al. and would therefore function in a manner taught by the prior art, thus rendering applicant's claims prima facie obvious in the event that the claim is not anticipated by the prior art.

B. Claims 24-29, 34-37, 42-47 and 52-56 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Kumagaye et al (J. Chrom. 327:327) or Kimura et al. (BBRC 114:493) or Fairwell et al. (Biochem. 22:2691). The three references all disclose hPTH which was synthetically made and purified to at least 95% purity; the teachings of each are outlined in the above rejection of these claims under 35 U.S.C. §102(b). The claims differ from the cited references only in that the claims are product-by-process claims, in which a different process than those used in the cited prior art is used. In the absence of evidence to the contrary, the claimed protein itself appears to be anticipated by the prior art, or alternatively is considered to be *prima facie* obvious over the prior art proteins, for reasons cited in the preceding paragraph.

7. Claim Rejections - 35 USC § 101 – provisional obviousness-type double patenting

Claims 24-29, 34-37, 42-47 and 52-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 31-35 of copending Application No. 08/340;664. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: hPTH(1-84) which can be recombinantly produced using E. coli or yeast. The '332 application claims compositions comprising PTH whereas the '664 application does not recite compositions. Furthermore, claim 31 of the '664 application does not recite that the protein has to be produced recombinantly and can, therefore, be contaminated by human proteins. However, the claims of the present invention do not recite "purified hPTH," but, rather, "compositions comprising hPTH." Therefore, even if the hPTH of the present invention was purified 100%, once it is placed into a composition, the presence of other contaminants, including human contaminants that may be present in the compositions of the '332, thereby meeting the limitations of the '664 application. Furthermore, the recitation in the '664 application of "having a purity of greater than 95%" would meet the limitation of the '332 application of "greater than 90%."

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
January 14, 2002

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER